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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/03/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,659	WHITTY ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication app ars on the cov r sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2002 and 02 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *19-22,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18, 23-25 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 4/11/01 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-9, 28, 29 and 31 in Paper No: 9 (6/25/02) is acknowledged. The traversal is on the ground(s) that Groups I and II can be searched and examined simultaneously. This is found to be persuasive. Therefore the Office will combine Groups I and II. Thus claims1-18, 23-25 and 28-31 will be examined.

Claims 19-22, 26 and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9 (6/25/02). Applicant further elected the species human IFNbeta-1a fused to human IgG1-Fc (hinge, CH2 and CH3 domains) in Paper No: 12 without traverse.

Specification

2a. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

2b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Drawings

3. The drawings have been approved by the draftsperson. Although, Applicant has numbered Figure 2 as Figs. 2A-1, 2A-2 and 2B, the legend does not reflect this.

Appropriate correction is required. Also check the numbering for the DNA sequence on page: 5, line 2.

Claim Objections

4. Claim 6 is objected to because of the following informalities: The claim has two periods. The claim needs to read .....a constant region of an immunogobulin. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 1, 3, 6-10, 12, 15-18 and 28-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes the mutations in Table 1(A1, A2, AB1, AB2, AB3, B1, B2, C1, C2, CD1, CD2, D, DE1, DE2 and E) for human IFN-β. Applicant has provided activities for some of these mutants. Specifically, activity has been recited for C1, D, DE1, A1, B2, CD2 (pages: 44 and 45). It is unclear if all the mutants described in Table 1 of the specification have activity (page: 35). Other than the mutations described on page 35, the specification does not disclose all the mutants or portions thereof the

polypeptide. The claims as written, however, encompass mutants and portions of the polypeptide which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 1, 3, 6-10, 12, 15-18 and 28-31. The specification does not provide written description for the following term: mutant and portions of the polypeptide. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

As a result, it does not appear that the inventors were in possession of invention to use the different mutations or portions of the polypeptide set forth in claims 1, 3, 6-10, 12, 15-18 and 28-31.

5b. Claims 1, 3, 6-10, 12, 15-18 and 28-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mutant human IFN-β described on page: 35 does not reasonably provide enablement for other mutant human IFN-β's or portion of the polypeptide. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Claims 1, 3, 6-10, 12, 15-18 and 28-31 have an overly broad recitation of "portions thereof" and "mutant human IFN-β". The Applicant describes the mutations in Table 1(A1, A2, AB1, AB2, AB3, B1, B2, C1, C2, CD1, CD2, D, DE1, DE2 and E) for human IFN-β. Applicant has also provided activities for some of these mutants. Specifically, activity has been recited for C1, D, DE1, A1, B2, CD2 (pages: 44 and 45). It is unclear if all the mutants described in Table 1 of the specification or portions of the polypeptides contemplated have activity (page: 35).

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions and

portions of the polypeptides are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made or portions generated with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active mutants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

A large quantity of experimentation would have been necessary for the skilled artisan to generate the infinite number of mutant human IFN-β or portions of the polypeptide recited in the claims and possibly screen the same for a useful activity. The specification fails to provide sufficient direction/guidance regarding which structural

features are required in order to provide mutant human IFN-β or portion of the polypeptide with activity. The nature of the invention is complex, involving the generation of mutant human IFN-β or portion and screening them for a useful activity. The state of the prior art establishes the unpredictability of the effects of mutation on protein structure and function. Finally, the breadth of the claims is large, failing to recite any structural or functional limitations for the recited mutant human IFN-β or portions of the polypeptides. For all of these reasons, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Given the breadth of claims 1, 3, 6-10, 12, 15-18 and 28-31 in light of the unpredictability of the art as determined by the confusing working examples, the level of skill of the artisan, and the lack of guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention of mutant human IFN-β or portion thereof.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6-10, 12, 15-18 and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6a. Claims 1, 6-10 and 15-18 rejected as vague and indefinite for reciting the term "portion thereof", because the specification does not clearly define the term "portion

thereof". It is unclear what portion comprising the interferon β polypeptide Applicant intends to use in the instant invention.

6b.Claims 3, 12 and 28-31 rejected as vague and indefinite for reciting the term "mutant", because the specification does not clearly define the term "mutant". The mutant described could be deletion, substitution, addition of a single amino acid or more than one amino acid. In addition, Applicant is functionally describing the mutant.

6c. Claim 29 and 31 are rejected as vague and indefinite because these composition claims are dependent on a method claim 27. Correcting the dependence of the claims can obviate this rejection.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7a. Claims 1-18, 23-25 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (U. S. Patent No. 5,908,626) and Bell et al. (U. S. Patent No. 4,914,033) in view of Carpon et al. (U. S. Patent No. 5,116,964) and Katre et al. (U. S. Patent No. 4,766,106).

Chang et al. disclose a hybrid recombinant protein consisting of human interferon-β and a human immunoglobulin Fc fragment (abstract). The reference teaches that a fusion protein generated in combination with Fc portion of immunoglobulins increases the half-life of the interferons (column 1, lines 41-57). It also teaches the advantage of producing this fusion protein in a mammalian expression system in order to have it glycosylated (column 3, line 31- column 4, line 9). Further, it teaches the measuring of the activity of the hybrid protein including an antiviral assay (column 4, line 16-30). However, the reference does not expressly teach the mutation of interferon-β to affect the antiviral activity and the proliferative activity. The reference also does not teach the conjugation of polyalkylglycol polymer. Although, the reference broadly teaches a fusion protein with the Fc region, it does not teach the constant region of the immunoglobulin comprising at least a hinge, CH2 and CH3 domains.

The Bell et al. reference teaches the mutation of interferon-β in order to increase the antiviral and/or antiproliferative and/or immunostimulating activities (column 5, lines 8-23).

Caphon et al. is relied upon as it describes the generation of fusion proteins with at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin (column 10, lines 10-13). The reference also describes that the

preferable immunoglobulin combining site for fusion partner is obtained from IgG1 (column 14, lines 65-67, also see Figure 8).

Katre et al. teaches that means for conjugating interferon -β to polymers to increase the solubility of these proteins without affecting their biological activity were known in the art. The reference teaches covalent conjugation of protein to a water-soluble polymer selected from the group consisting of polyethylene glycol, homopolymers, and polyoxyethylated polyols (column 4, lines 26-29). It also teaches pharmaceutical compositions comprising the conjugated IFNs (column 4, lines 42-58).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to generate fusion proteins of both wild type and mutated human IFN-β fused to IgG1-Fc, as described by Caphon et al, because Bell et al. teaches that mutating the human IFN-β at specific positions increase the antiviral and/or antiproliferative and/or immunostimulating activities; furthermore Katre et al. teaches the pegylation of interferon -β to increase the solubility. One of ordinary skill in the art would have been motivated to pegylate human IFN-β (wild type and mutated) to produce a polyalkylglycol polymer conjugated IFN fusion protein containing the Fc portion of immunoglobulins which retains it biological activity. Thus the claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary. Therefore, the instant invention is obvious over Chang et al. (U. S. Patent No. 5,908,626) and Bell et al. (U. S. Patent No. 4,914,033) in view of Carpon et al. (U. S. Patent No. 5,116,964) and Katre et al. (U. S. Patent No. 4,766,106).

8. No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS
December 2, 2002

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